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AdvaMed
Advanced Medical Technology Association

June 4, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket # 01N-0322 – "Institutional Review Boards: Requiring Sponsors and Investigators to Inform IRBs of Any Prior IRB Reviews"

Dear Madam/Sir:

AdvaMed is pleased to provide comments on the Advance Notice of Proposed FDA Rulemaking that would require sponsors and investigators to inform IRBs of any prior IRB reviews. AdvaMed, the Advanced Medical Technology Association represents more than 800 innovators and manufacturers of medical devices, diagnostic products and medical information systems. Our members produce nearly 90 percent of the $68 billion in health care technology products consumed yearly in the United States and nearly 50 percent of the $159 billion purchased around the world annually.

AdvaMed has a number of comments, both general and specific, discussed below:

General Comments
As innovators and manufacturers of medical technology, AdvaMed member companies sponsor clinical research and understand the importance of ensuring the integrity of the Institutional Review Board (IRB) process. The regulated functions of an IRB are to formally review, approve the initiation of, and conduct periodic review of biomedical research involving human subjects [see 21 CFR 56.102(g)] to protect the rights and welfare of human subjects.

We recognize that the objective of a rulemaking to require sponsors and investigators to inform IRBs of prior IRB reviews would be to ensure that sponsors and clinical investigators who submit protocols to more than one IRB would not be able to ignore an unfavorable IRB review. Another would be to improve Federal oversight of IRBs and to gather information regarding the level of significance related to the practice of IRB shopping.

AdvaMed, however, does not believe that the changes that are contemplated will satisfy the concerns raised by the Office of the Inspector General (OIG). They would, however, induce needless burdens on IRBs, sponsors, and clinical investigators. If implemented, such changes

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would be confusing and would not likely positively affect human subject protection. They would create major obstacles, delays and increased costs to research efforts to develop life-saving, life-enhancing technologies for patients.

Current Regulations Provide Appropriate Human Subject Protections

AdvaMed believes that existing regulations provide appropriate human subject protections.

Investigational Device Exemption Regulations

The Investigational Device Exemption (IDE) regulations apply to studies involving significant risk devices.

- 21 CFR 812.20 requires the sponsor to submit as part of its IDE application a listing "of each IRB that has or will be asked to review the investigation along with a certification of the action taken by each such IRB" [21 CFR 812.20(b)(6)].

- 21 CFR 812.27 requires the IDE application to include reports and a comprehensive summary of prior investigations "whether adverse or supportive". Disapproval of a study by a previous IRB would be required to be disclosed to FDA under this regulation.

- 21 CFR 812.35(a) requires that any changes to an investigational plan must receive IRB approval: "a sponsor must obtain . . . IRB approval when appropriate . . . prior to implementing a change in an investigational plan.

- 21 CFR 812.40 requires sponsors to ensure "IRB review and approval are obtained . . . and ensuring that any reviewing IRB and [that] FDA are promptly informed of significant new information about an investigation." Under this requirement, sponsors must determine whether any significant modification requested by one IRB must be made at all study sites.

- 21 CFR 812.42 provides additional protections and requires that, "a sponsor shall not begin an investigation or part of an investigation until an IRB and FDA have both approved the application or supplemental application relating to the investigation or part of an investigation." This requirement ensures a detailed review of the protocol and investigational plan to protect patients' rights and welfare before a study may begin.

- In the event that an IRB withdraws its approval after a study has begun, 21 CFR 812.150(b)(2) requires sponsors to notify both "FDA and all participating IRBs and participating investigators of any withdrawal of approval of an investigation if one IRB withdraws its approval of the studies within 5 working days after receipt of the withdrawal of approval."

- Another existing human subject safeguard is 21 CFR 812.150(b)(9) which requires that, "If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination."

In summary, sponsors must notify FDA of any IRB review decisions (and other IRBs if an IRB approval is withdrawn) and provide FDA with the IRB certifications. FDA then makes a final determination that is enforced across all study sites. Through FDA's review and approval of significant risk studies, it can impose any form of IRB notification it chooses.

Institutional Review Board (IRB) Regulations

For both significant risk and non-significant risk studies, the current IRB regulation, 21 CFR 56, is also adequate since it clearly places the burden for ensuring patient protection on each IRB.

- The regulations require each individual IRB to perform its own risk/benefit analysis of each proposed (21 CFR 56.111) study and determine what information and data the study sponsor and investigator(s) should supply.

- Each IRB must establish written procedures that describe its risk analysis process (21 CFR 56.108).

- To approve research covered by these regulations (21 CFR 56.111), the IRB must determine that all of the following requirements have been satisfied:
    1. Risks to subjects are minimized.
    2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result.
    3. Selection of subjects is equitable.
    4. Informed consent will be sought from each prospective subject or their legally authorized representative.
    5. Informed consent will be appropriately documented.
    6. Where appropriate, the research plan makes adequate provision for monitoring the collected data to ensure the safety of the subjects.
    7. Where appropriate, there are adequate provisions to protect the privacy of the subjects and to maintain the confidentiality of data.

- The IRB must have and "follow written procedures for ensuring prompt reporting to . . . the Food and Drug Administration of: . . . any unanticipated problems involving risks to human subjects or others . . . or any suspension or termination of IRB approval (21 CFR 56.108(b)).

- Finally, the IRB has explicit "authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected harm to subjects." (21 CFR 56.113)

Providing that IRBs are complying with these regulations, there is no need to add additional burdensome requirements. Additionally, in the vast majority of non-significant risk studies, the risk to patient safety is so low that there is little incentive to forum shop.

In summary, AdvaMed believes the existing regulations for both significant risk and non-significant risk device studies provide meaningful directives to adequately protect patients.

Overly Burdensome and Administratively Difficult to Implement
Imposing a rule that requires the sponsor to notify all IRBs of any prior IRB review decisions is burdensome and would be administratively unworkable. Many medical device investigations involve multiple centers. Under such rules, a new study requirement could be imposed by the last IRB that reviewed the proposed study, causing all the other IRBs to re-review the proposal. This would add burden to a system that the OIG reports is already stressed due to "expanded workloads, resource constraints, and extensive Federal mandates." (June 1998 OEI-01-07-97-00193).

Such rules could also create incentives for IRBs to delay study approvals because another IRB might make a different determination. Additionally, the objective decision-making of a smaller institution's IRB could be influenced by learning that one or more large, renowned educational institutions have previously approved a study.

Non-significant risk studies involving medical devices, especially in vitro diagnostic products (IVDs), can also be somewhat fluid. To expedite the overall evaluation or to further challenge the study hypothesis, sponsors sometimes add to their list of active investigators after the initial investigators have begun collecting data. AdvaMed can foresee scenarios where a new IRB might impose requirements for its site that may not be necessary for other sites. What would be required of the sponsor in these situations? Would it be required to immediately stop the multi-center study until each of the other responsible IRBs consider the requirements imposed by the new IRB? What if other centers have already finished their portions of the study?

IRB Shopping Occurs for Reasons Unrelated to Patient Safety
IRBs may, and frequently do, reach different determinations on clinical trials for legitimate reasons unrelated to patient safety. In fact, IRB regulations (21 CFR 56.107(a)) require IRB membership and IRBs to be sensitive to community attitudes. Other reasons that studies may be disapproved or that sponsors may seek out other IRBs include:

- differences in regional medical practice,
- the need for a varied population mix in a study
- hospital policy, and
- the inability of a sponsor and an IRB to agree on IRB fees, a study budget or the terms of indemnification.

Thus, sponsors and investigators may legitimately seek out other IRBs for reasons that are unrelated to patient safety.

Question 1: FDA asks how significant is the problem of IRB shopping?
The ANPRM references the June 1998 OIG report which states that the OIG had ". . . heard of a few situations where sponsors and/or research investigators who were unhappy with one IRB's reviews switched to another without the new IRB being aware of the other's prior involvement," but notes that the OIG report does not quantify the number of situations where this occurred. Also, it is not clear whether:

- these situations were related to clinical trials regulated by FDA or clinical trials regulated by Health and Human Services (HHS),
- the studies were significant risk or non-significant risk studies, or

- the sponsors or investigators switched for reasons unrelated to patient safety.

Many medical device studies require the expertise of a highly focused specialist. In these cases, medical device manufacturers choose investigational sites based on the availability of skilled, knowledgeable investigators. The IRB affiliation of an investigator is not typically a determinant in investigational site selection except in cases where there is a roadblock like an inability to agree upon a study budget, an unreasonable request for indemnification, or excessive IRB fees are required for study review. Note that none of these determinants are related to patient safety.

Additionally, as a matter of practice, some sponsors may submit protocols to IRBs for more clinical sites than they intend to use so that the clinical study is not delayed due to an overburdened or slowly responding IRB. The study is then conducted at the first number of sites that obtain IRB approval.

> ***AdvaMed Response***
> AdvaMed does not believe that forum shopping is a significant problem, particularly since FDA is an active partner in device studies involving significant risk. And, in the vast majority of non-significant risk studies, the risk to patient safety is so low there is little incentive to forum shop. This may not be the case with studies overseen by HHS.

Question 2: FDA asks who should be required to make disclosures?
In many cases, investigators do not know the other investigators or IRBs involved. Additionally, each investigator is bound by confidentiality agreements and therefore cannot discuss the studies with persons not bound by the agreement. This is not the case if the investigator is also the sponsor and initiates and conducts the study.

Importantly, under current practice when an IRB requests a modification to a study, the *sponsor* must determine whether the modification should be made at all study sites or whether it is a local, site-specific issue (see 21 CFR 812.35(a) – Changes to an Investigational Plan). Under the regulations, IRBs are required to make appropriate decisions for their institution. However, that does not mean that all other sites must follow their recommendations. In these situations, it is the sponsor's responsibility to provide the appropriate notifications to other IRBs.

> ***AdvaMed Response***
> AdvaMed does not believe IRB forum shopping is a problem. In addition, AdvaMed believes that a rule in this area will be difficult to implement because it appears the ANPRM contemplates extending reporting from that related to forum shopping to general reporting of IRB decisions. Nevertheless, should FDA proceed in this area, disclosure responsibility should lie with the sponsor for the reasons noted above.

Questions 3 and 4: FDA asks who should receive the disclosures? What information should be disclosed?
In this question, FDA extends the reporting issue from one directly related to opinion shopping to general reporting of IRB decisions. In addition to providing attentive patient care, investigational sites must track a number of documents related to each study, including their own IRB approval letters. FDA's example of Investigators X and Y aptly illustrates the

administrative problems in implementing any reporting system, particularly reporting of information that goes beyond informing IRBs when another IRB has withdrawn approval of a study.

Potentially requiring each investigational site to monitor and track all other sites' IRB approval letters will place needless and substantial burden on investigational sites. The proposal would impose upon the IRB additional responsibility for the reviews previously completed *and* subsequently completed by all other participating IRBs. The question also creates additional concerns about obligations and responsibilities. For example, if one IRB disapproves or poses limitations after information has been submitted to a second IRB but before the second IRB has made a final decision, what is the sponsor's obligation?

IRBs may disapprove studies for reasons that may be totally unrelated to patient safety, rights or welfare. Any additional regulation that addresses the concerns as stated by the OIG, assuming that any unfavorable IRB opinions (in a multi-center study) indicate unacceptable risk to patients, would require IRBs to complete a *concurrent* review with coordinated approval or rejection of all studies.

Furthermore, a site's IRB may potentially require specific conditions of approval unique to its institution related to an individual investigator's study participation or site-specific focus areas or to region-specific requirements. Under the regulations, IRBs have the right to require conditions above and beyond what is submitted to ensure adequate informed consent and patient protection. For example 21 CFR 56.109(b) allows the IRB to ". . . require that information, in addition to that specifically mentioned in 50.25, be given to the subjects when in the IRB's judgement the information would meaningfully add to the protection and welfare of subjects." 21 CFR 56.109(e) requires IRBs to "notify investigators and the institution . . . of modifications required to secure IRB approval of the research activity." However, these additional conditions should not necessarily be mandated for other participating sites to follow, since they may be investigator-specific or region-specific requirements the IRB is following. In these situations, sponsors may need to protect the privacy of a particular investigator or institution and it may be inappropriate for sponsors to disclose sensitive, internal institution or investigator-specific information to other IRBs.

Finally, tracking the IRB decision letters from potentially 30 or more IRBs per study is not an effective use of time for investigational sites. The presence or lack of study approval decision letters from each IRB participating in a study would potentially be auditable by regulatory agencies. Sponsors and IRBs could be exposed to issues of continuous noncompliance for administrative reasons only.

AdvaMed Response
AdvaMed does not believe IRB forum shopping is a problem. In addition, AdvaMed believes that a rule in this area would be difficult to implement for the reasons above. Nevertheless, should FDA proceed in this area, disclosure responsibilities should lie with the sponsor to report to other IRBs when an IRB has disapproved a study and the reasons why. Sponsors should also have the opportunity to explain what actions, if any, were taken to overcome the objection of the prior IRB or why it believes the IRB should have granted a positive decision.

Questions 5 and 6: FDA asks if a proposal would not require disclosure of all prior IRB decisions, what information should be disclosed? To permit a subsequent IRB to assess the value of a prior IRB decision, should information about the basis for the prior decision be disclosed?

It is the sponsor's responsibility to decide whether or not IRB-requested modifications need to be implemented across all study sites. This is especially true because prior IRB decisions may be based upon different protocols or different versions of the product and may have no bearing on the protocol under current review. The sponsor should use a protocol amendment to disclose to each affected investigator any information relative to the current protocol. Questions from IRBs regarding reasons for protocol amendments should be answered on an individual, as-needed basis.

AdvaMed Response

AdvaMed does not believe IRB forum shopping is a problem. In addition, AdvaMed believes that a rule in this area would be difficult to implement for the reasons above. Nevertheless, should FDA proceed in this area, IRB disapproval decisions should continue to be provided to the sponsor along with detailed reasons for the disapproval. It is then the responsibility of the sponsor to share the information with other IRBs reviewing the protocol.

Question 7: FDA asks how should FDA enforce the requirement?

Pursuit of the proposed regulations would in all likelihood lead sponsors to over-report and provide continual reporting of information whether it is relevant or not in order to avoid noncompliance and enforcement actions.

AdvaMed Response

AdvaMed does not believe IRB forum shopping is a problem. In addition, AdvaMed believes that a rule in this area would be difficult to implement for the reasons above. Nevertheless, should FDA proceed in this area, FDA could enforce such rules during the product review process (see below), or through Bioresearch Monitoring audits of IRBs. Similarly, FDA could request copies of all disapproved protocols from IRBs and take further action if it detects forum shopping.

Question 8: FDA asks if there are other ways to deal with IRB shopping other than disclosure of prior IRB reviews?

As a matter of practice, a number of major IRBs already ask sponsors to provide information regarding review by other IRBs when the trials have been disapproved, or a prior IRB approval has been withdrawn, or terminated. The IRBs that currently require such disclosure enforce the requirement by not processing any submission that fails to supply a complete submission form. IRBs can and do withhold approval for those sponsors and investigators who fail to comply.

The June 1998 HHS OIG report acknowledged that there were only "a few situations" where IRB shopping presumably occurred. Because current regulations provide more than adequate human subject protection, including requirements that all IRBs be informed when an IRB withdraws approval [21 CFR 812.150(b)(2)], AdvaMed suggests that FDA not promulgate regulations in this area and that sponsors continue to retain the responsibility to determine

when a particular IRB's protocol modification needs to be implemented at other sites and to report IRB disapprovals as part of its IDE application [21 CFR 812.20(b)(6)] for significant risk device studies. As referenced in the answer to questions 3 and 4, it is the sponsor's responsibility to determine when a modification proposed by an IRB is site or region-specific. Additionally, an IRB may condition study approval on a modification of the study plan. Again, it is the sponsor's responsibility to determine whether such a modification should be made at all study sites (21 CFR 812.40).

FDA's energy would be more effectively targeted to fostering information sharing among IRBs as well as harmonizing IRB standards. The Department of Health and Human Services could also consider applying the language and requirements in 21 CFR 812 to all clinical studies regulated by its various agencies.

> ***AdvaMed Response***
> Nevertheless, should FDA proceed in this area, AdvaMed suggests that FDA could alternatively build a reporting mechanism into submissions having clinical data. For example, IDE regulation 21 CFR 812.20 requires sponsors to provide "a list of the name, address and chairperson of each IRB that has been or will be asked to review the investigation." FDA could then ask each sponsor to prepare a table matching each participating study site with its respective IRB. If study sites associated with a particular IRB are not used, the sponsor could be asked to provide the reasoning for not including those sites in the study. Such a process would reveal whether the failure to use a particular study site was for legitimate reasons (e.g., an inability to recruit patients) or was potentially related to IRB shopping. This would be more effective than reporting IRB decision-making results to all participating IRBs. As the OIG report concluded, IRBs are already overburdened and FDA is in a better position to determine whether the specific facts warrant further action.

Conclusion

In closing, AdvaMed believes that the existing regulations provide appropriate human subject protections and that the changes in the rules that are being contemplated will not satisfy the concerns raised by the OIG. The changes would, however, induce needless burdens on IRBs, sponsors, and clinical investigators. They would be confusing and would not add significantly to already existing human subject protection regulations. They would, however, create major obstacles, delays and increased costs to research efforts to develop life-saving, life-enhancing technologies for patients.

AdvaMed is pleased to have had the opportunity to submit comments on FDA's proposed rules for IRB forum shopping. Please don't hesitate to contact me at 202/434-7208.

Sincerely,

Tara Federici

Tara Federici, Associate Vice President
Technology & Regulatory Affairs

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Dockets Management Branch

May 10, 2002

Re: Docket No. 01N-0322

To Whom It May Concern:

The investigators and coordinators of the Public Access Defibrillation (PAD) Trial support and encourage the ethical conduct of research. IRB review is the cornerstone of the oversight that assures this ethical imperative. The practice of "IRB shopping" threatens to compromise the integrity of this process. Thus, the PAD investigators concur that IRBs should have full knowledge of any prior unfavorable IRB reviews when asked to review the same or an essentially similar protocol.

However, we are concerned about the practical implications of the proposed rule as it would apply to multicenter trials like ours. The PAD trial was initially reviewed and approved by the University of Washington IRB (Seattle, WA) and then by the applicable IRB at each of the 24 participating sites. Approval was then sought from hospitals that might receive enrolled subjects. This has involved protocol submission to date to 101 IRBs and has resulted in at least 50 requests for revisions. We believe that requiring all IRBs to be notified of all the decisions of all other IRBs involved in a multicenter trial would impose a tremendous, if not impossible, burden without adding significant protection to subjects.

We do, however, propose a process for multicenter trials that should achieve the desired goal. We suggest that negative final decisions (or investigator withdrawal because of likely denial) be reported in hierarchical fashion. Denial by a site or secondary IRB would be reported to the primary IRB for the multicenter trial. (Figure) Denial by, for example, a community hospital IRB (a tertiary IRB) would be reported to the site IRB, and so on. The IRB receiving such notification would then review the reporting IRB's rationale and concerns, review the approved protocol and determine if the issues raised by the denying IRB required action, such as protocol modification and/or notification of other IRBs involved in the trial. Importantly, simultaneous (or near simultaneous) submission to multiple hospital IRBs at a particular site after approval by the primary (coordinating center) and the site (secondary) IRBs should not be considered "IRB shopping."

As the request for comments states, some process issues will need to be addressed as well, including who makes the report, what should be reported, and when to report. It seems reasonable that investigators should be obliged to report, but also requiring the denying IRB to report to the appropriate hierarchical IRB as described above would help to promote compliance. We believe only final negative decisions and protocol withdrawals should be required to be reported, although it would seem advantageous for investigators to report prior approval. The report should indicate the reason for the denial so that the IRB can determine the need for any further action. For ongoing trials, a negative review at a secondary or tertiary site would be reportable immediately to the appropriate IRB as described above.

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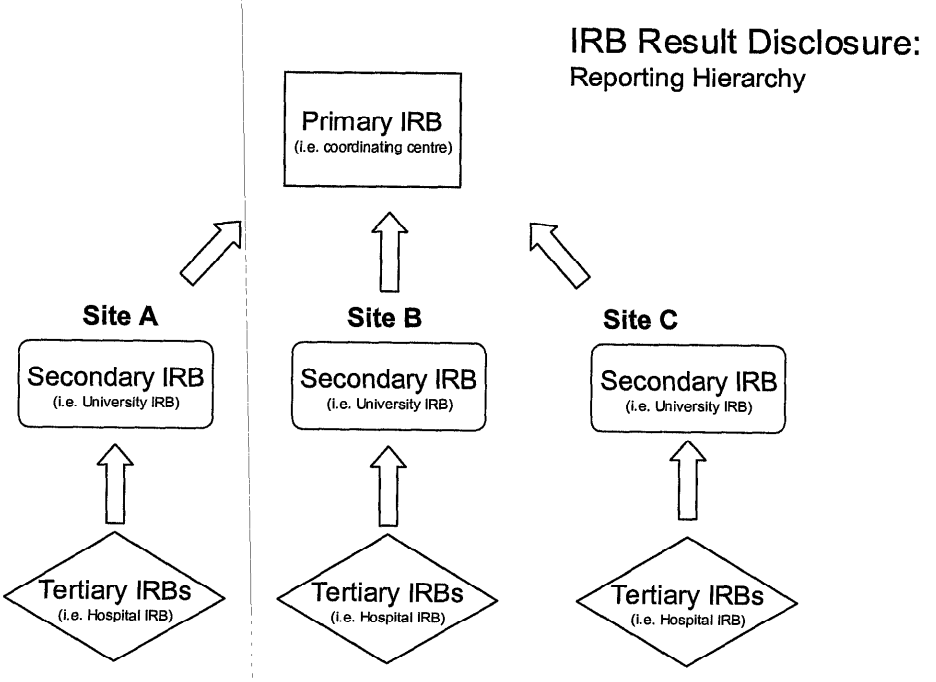
For the initial submission of a multicenter trial to a primary IRB, that submission and any action should be treated like a single site study, with full disclosure of any denial to any other IRBs if the study is resubmitted elsewhere for primary IRB approval.

In summary, based on our experience with a large multicenter trial, we feel strongly that safeguards against the potentially unethical practice of "IRB shopping" may be warranted but must be carefully crafted to avoid being unreasonably burdensome or even untenable in the setting of a multicenter trial involving a large number of IRBs often simultaneously reviewing and seeking revisions of the same protocol. We have proposed a process that we believe would provide appropriate reporting and review of negative decisions without excessive burden.

Sincerely,

Joseph P. Ornato, M.D.
PAD Executive Committee Chair

Figure.



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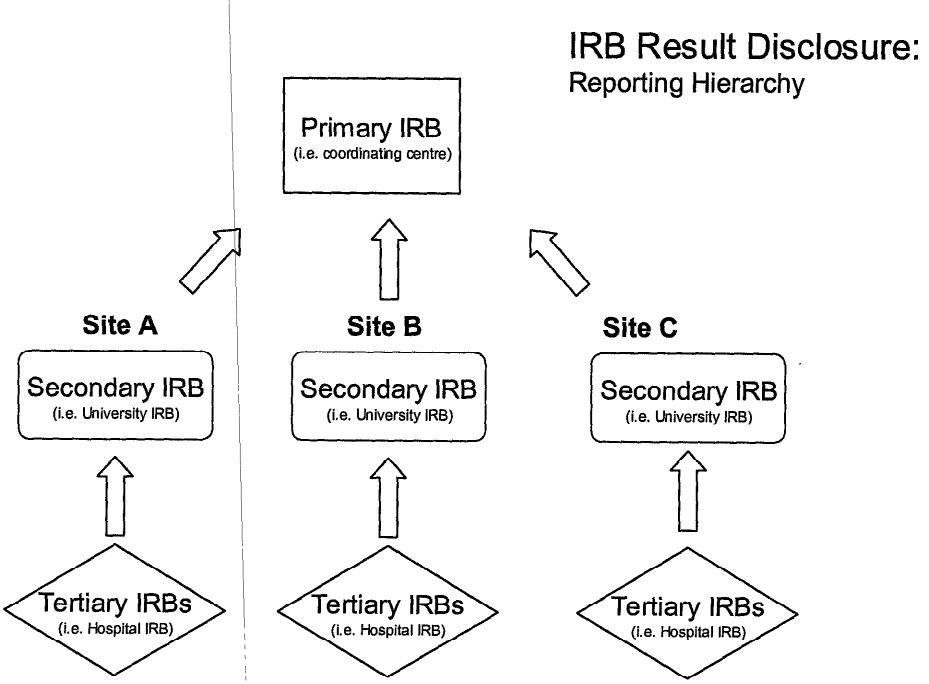

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